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## ORIGINAL CLINICAL SCIENCE STUDIES

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# In situ replacement of infected aortic grafts with rifampicin-bonded prostheses: The Leicester experience (1992 to 1998)

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**Purpose:** Prosthetic graft infection after aortic aneurysm surgery is a life-threatening complication. Treatment options include total graft excision and extra-anatomic bypass grafting or in situ replacement of the graft. The latter option is gaining increasing popularity, but the long-term outcome remains uncertain, particularly in light of the increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA). We performed a prospective nonrandomized study to assess the outcome after graft excision and in situ replacement with a rifampicin-bonded prosthesis for the treatment of major aortic graft infection.

**Methods:** In a 6-year period from January 1992 to December 1997, 11 patients (eight men, three women) with major aortic graft infection underwent total graft excision and in situ replacement with a rifampicin-bonded prosthesis. The median age of the patients was 66 years (range, 49 to 78 years). Four patients had a hemorrhage from an aortoenteric fistula, three had a retroperitoneal abscess, two had graft occlusion, one had a perigraft collection shown by means of computed tomography, and one had a ruptured suprarenal false aneurysm. Organisms were cultured from 10 patients.

**Results:** MRSA was isolated in two patients, both of whom had originally undergone repair of a ruptured abdominal aortic aneurysm. Two patients died (18.2%) within 30 days, and three patients (27.6%) had nonfatal complications (peritoneal candidiasis, transient renal impairment, and profound anorexia). Two patients died late in the follow-up period. Seven patients remain alive and clinically free of infection.

**Conclusion:** The long-term results after total graft excision and in situ replacement with a rifampicin-bonded prosthesis appear to be favorable. However, MRSA aortic graft infection appears to be associated with a poor prognosis. (*J Vasc Surg* 1999;30:92-8.)

There has been a natural reluctance to treat major aortic graft infection (MAGI) with total graft excision (TGE) and in situ revascularization, because of the risk of reinfection. However, although this probably applies to standard prostheses, there is increasing evidence that in situ replacement with an antibiotic-bonded graft confers the benefits of anatomical reconstruction (higher flow, enhanced patency, maintenance

of internal iliac circulation), while avoiding the problems of TGE and extra-anatomical bypass grafting (longer procedure, lower flow, poorer patency, gluteal ischemia, aortic stump blowout) and without incurring the inevitable risk of secondary infection.<sup>1-3</sup> Moreover, for those patients in whom the infective process involves the suprarenal vessels, extra-anatomical bypass grafting is not an option, and some form of anatomical revascularization is unavoidable.

After Strachan's initial report of using a rifampicin-bonded prosthesis,<sup>4</sup> we reported our preliminary experience of five patients who had MAGI and were successfully treated with this technique.<sup>3</sup> Our experience has now increased to 11 patients, and this report highlights the evolving modifications to our operative technique, early and late outcomes, and the problems associated with the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) graft infections.

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## MATERIALS AND METHODS

**Preoperative assessment.** Between Jan 1, 1992, and Dec 31, 1997, 11 patients with MAGI underwent TGE and in situ revascularization with a rifampicin-bonded prosthesis. During the same period, one other patient with MAGI underwent TGE and an extra-anatomical bypass grafting procedure (surgeon preference), but this patient died in the early postoperative period. All patients were treated with intravenous cefuroxime and metronidazole when the diagnosis of MAGI was suspected, but this treatment was revised if subsequent cultures revealed resistant organisms. Those patients who had acute emergencies (eg, massive gastrointestinal hemorrhage) did not undergo any preoperative investigations. The remainder underwent preoperative computed tomography (CT) scanning, but angiography was only used at the discretion of the operating surgeon. With regard to the duration of infection, seven of the 11 patients had acute emergencies with no earlier illness. The range of earlier illness in the remaining four patients was 5 to 17 days.

**Operative technique.** The first priority was control of the diaphragmatic aorta to prevent uncontrollable hemorrhage during the procedure. After this, the juxtarenal aorta was exposed either by means of reflection of the right colon, duodenum, and pancreatic head medially or by means of medial visceral rotation of the spleen, stomach, left colon, pancreas, and left kidney. No attempt was made to directly expose the aorta or graft through the retroperitoneal inflammatory mass. By using the above approaches, it is usually possible to mobilize a segment of the aorta immediately below the renal arteries that is not involved in the inflammatory process. However, for those with juxtarenal involvement, the suprarenal aorta and renal arteries were mobilized, allowing insertion of balloon irrigation catheters in the renal artery orifices to allow cold perfusion of the kidneys while the suprarenal aorta was clamped.<sup>5</sup> An important modification to our original technique has been used in patients with massive gastrointestinal hemorrhage and involves inflation of an aortic balloon catheter (inserted via the femoral artery) at the level of the proximal false aneurysm. Once this has been achieved, dissection can proceed in a more controlled manner while the anesthetist stabilizes the patient.

Once proximal control was achieved, the distal anastomoses were mobilized, and the patient was systemically treated with heparin (5000 IU). The aorta was then cross-clamped, and the aorta/graft was opened posterolaterally or posteromedially (ie,

well away from the inflammatory mass). Any defect in the bowel was then repaired or resected, as appropriate. A presized gelatin-impregnated Dacron prosthesis (Gelsoft, Vascutek, UK) was then irrigated with 600 mg rifampicin, which had been reconstituted in 10 to 15 mL sterile water.

The graft was left to soak in the rifampicin solution for 20 minutes in the manner described by Strachan<sup>4</sup>; during this time, the original graft was excised entirely, specimens of graft, anastomosis, and perigraft tissue was sent for microbiological culture, and the retroperitoneum was debrided. It can often be difficult to identify the ureters in the inflammatory mass, therefore the tunnel tracks were debrided as much as was safely possible and then irrigated with aqueous iodine. The new prosthesis was then tunneled and anastomosed in the usual manner. After this was completed, the graft was covered with retroperitoneum, omentum, or both where possible; specific care was taken to exclude the bowel from the graft. In four patients, Foley catheters were also placed within the retroperitoneum to permit postoperative antibiotic irrigation, in the manner described by Quick.<sup>6</sup> These remained in situ for 10 days or until there was resistance to injection.

**Postoperative care.** Systemic antibiotics were continued for 2 weeks postoperatively. Only in the two patients in whom MRSA was isolated did the original systemic antibiotic therapy have to be changed. Thereafter, the patient was changed to an appropriate oral antibiotic regimen for 6 more weeks. The decision to stop antibiotic therapy at 6 weeks was based on microbiological advice, provided there was no evidence of ongoing infection, either on blood cultures or on a clinical basis. Patients found to have MRSA graft infections had a tunneled Hickman line inserted into a central vein and were prescribed systemic vancomycin or teicoplanin for 6 weeks, or until there was no evidence of ongoing systemic infection. Three to 6 months postoperatively, all survivors underwent a <sup>111</sup>Indium-labeled white cell scan to exclude residual infection.<sup>7,8</sup> Patients subsequently were examined in the outpatient clinic, but two were lost to follow-up, one at 12 months and one at 15 months, despite repeated letters to the patients and their family doctors.

## RESULTS

Eleven patients (eight men, three women) with a median age of 66 years (range, 49 to 78 years) underwent TGE plus in situ replacement with a rifampicin-bonded prosthesis for the treatment of MAGI. The original vascular procedure was elective

**Table I.** Thirty-day morbidity and mortality

Patient number	Age (years)	Reason for primary operation	Time since first graft (months)	Secondary presentation	Microbiology	Complications
1	67	Elective AAA	60	Pyrexia, sciatica, abdominal mass	<i>Streptococcus viridans</i>	None
2	75	Elective AAA	15	Graft occlusion, false aneurysm	<i>Escherichia coli</i>	None
3	68	ABG	4	Groin abscess, perigraft collection	<i>Streptococcus faecalis</i>	None
4	49	Elective AAA	64	Bleeding aortoenteric fistula	<i>Staphylococcus epidermidis</i> , <i>Streptococcus milleri</i> , <i>Haemophilus parainfluenzae</i>	Prolonged ileus, peritoneal candidiasis
5	65	Elective AAA	5	Ruptured proximal false aneurysm	<i>Staphylococcus epidermidis</i>	Renal impairment, no dialysis
6	78	Ruptured AAA	2	Graft-enteric fistula, psoas abscess, acute MI	<i>Escherichia coli</i>	Death caused by duodenal leak and biliary peritonitis
7	64	ABG	57	Graft-enteric fistula, septic emboli, false aneurysm	<i>Streptococcus faecalis</i>	None
8	69	ABG	120	Three false aneurysms	Negative cultures	None
9	46	Ruptured AAA	2	Psoas abscess	MRSA	Death caused by aortic candidiasis leading to rupture
10	70	Elective AAA	18	Septic shock	<i>Klebsiella pneumoniae</i> , <i>Streptococcus faecalis</i>	None
11	67	Ruptured AAA	4	Aortoenteric fistula	MRSA	None

AAA, Abdominal aortic aneurysm; ABG, aortobifemoral bypass graft; MI, myocardial infarction; MRSA, methicillin-resistant *Staphylococcus aureus*.

aneurysm repair in four patients and repair of a ruptured aneurysm in three, whereas four patients had undergone elective aortobifemoral bypass grafting procedures for occlusive disease. Five patients were treated within 6 months of their original surgery (including all those undergoing operation for ruptured aneurysm), two were treated within 6 to 12 months of their original surgery, and four were treated after 4 years or longer had elapsed.

Table I summarizes the clinical presentation and 30-day morbidity and mortality rates in the 11 patients, some of whom had multiple clinical features. Four of the 11 patients had acute emergencies, with massive hemorrhage from an aortoenteric fistula, and three patients had large retroperitoneal abscesses. Two patients had graft occlusion, one of which was in association with a false aneurysm of the proximal anastomosis. One patient had a perigraft collection, which on CT scan demonstrated an air-fluid interface. The remaining patient, who had undergone elective repair of an aneurysm 5 months earlier, had a ruptured suprarenal false aneurysm.

Bacteriological cultures yielded a number of different organisms from the 11 patients. Only one patient had a culture that was negative for bacteria (she had been on systemic antibiotics for 2 weeks preoperatively), whereas the remaining patients had one or more organisms cultured. However, unlike our initial experience,<sup>3</sup> two of the patients treated

later in our extended series had MRSA cultured from the excised grafts. Both of these patients had originally undergone emergency repair of a ruptured aortic aneurysm, both were treated for emergencies (one for acute myocardial infarction, aortoenteric fistula, and retroperitoneal abscess and one for collapse and infected retroperitoneal hematoma), and we were unaware of the bacteriological diagnosis for either patient before dealing with their infected grafts. One of the MRSA patients had retroperitoneal catheters inserted into an infected retroperitoneal hematoma at the time of TGE and in situ revascularization.

Two patients (18.2%) died within 30 days, and three patients (27.6%) sustained nonfatal complications. A 73-year-old man, who had undergone repair of a ruptured aneurysm 3 months earlier, had an aortoenteric fistula and a retroperitoneal abscess and died after sustaining biliary peritonitis. He initially went to another center with collapse and an acute myocardial infarction. The second death occurred in a 46-year-old woman who had an MRSA infection of a retroperitoneal hematoma after repair of a ruptured aneurysm 6 weeks earlier. This patient received systemic and retroperitoneal vancomycin for 26 days; but just before discharge, she sustained a cardiac arrest after a massive intraperitoneal hemorrhage. Despite aggressive resuscitation and a further TGE and axillobifemoral bypass grafting procedure,

she died. At autopsy, there was no evidence of any residual MRSA infection, but she had extensive retroperitoneal candidiasis and a candidal aortitis causing aortic rupture 1 cm above an intact proximal aortic anastomosis.

One other patient undergoing postoperative retroperitoneal antibiotic irrigation had peritoneal candidiasis, but it resolved after cessation of irrigation. One patient had a transient deterioration in renal function, but no patients in this series required dialysis or major limb amputation. The remaining complication of note was profound anorexia, which necessitated prolonged parenteral and then enteral feeding, in the surviving MRSA patient who had an infected hematoma after undergoing repair of a ruptured aneurysm 2 months earlier. As will be seen, we suspect that this was a manifestation of ongoing MRSA infection.

Of the nine survivors, seven remained alive and clinically free of infection; two survivors were lost to follow-up, one at 12 months and one at 15 months. The 1-year survival rate was 64%. Of the remaining five survivors, one has been asymptomatic for 75 months, three have been asymptomatic for more than 60 months, and one has remained clinically free of infection for 35 months. However, two of the 30-day survivors have subsequently died. The first (who had MRSA anorexia in the early postoperative period) died 4 months postoperatively of pneumonia. Although never proven at autopsy, we strongly suspect that this patient had an ongoing MRSA infection. The second patient who subsequently died originally had septic emboli in the right leg, a graft-enteric fistula (with gallstones lying on the right graft limb), and a bile-stained false aneurysm in the right groin. The left graft limb and groin looked normal, and because the left groin had been previously explored on a number of occasions, the first in situ revascularization was extended down to the left external iliac artery at the level of the inguinal ligament (ie, leaving a small portion of the original graft in the left groin). In retrospect, this was probably a mistake, because 12 months after his TGE and in situ revascularization, the patient had an apparently sterile left groin false aneurysm, which was treated by means of an obturator bypass graft. However, 8 months later (22 months after the first operation for MAGI), he had a bleeding aortoenteric fistula and underwent a further TGE with bipopliteal revascularization from his supraceliac aorta via both obturator foramina, but he died 2 weeks after this operation of acute respiratory distress syndrome and renal failure.

## DISCUSSION

Prosthetic graft infection is one of the most dreaded complications of vascular surgery. Overall rates for major graft infection average around 2%, ranging from less than 1% to 6% in published series.<sup>9-14</sup> The treatment of infected aortic grafts is difficult and is associated with high morbidity rates<sup>10,11,13,15,16</sup> and mortality rates.<sup>10,11,13,17</sup>

There are a number of important considerations when dealing with aortic graft infection. The primary objective is eradicating the underlying infection. The degree to which this can be achieved is limited by two factors: the need to maintain adequate peripheral perfusion while minimizing the morbidity and mortality in these compromised patients. Previously, there have been two schools of thought regarding management of aortic graft infection, the conservative approach and the radical approach. The conservative approach involved placing gentamicin beads in the infected field or adjacent to the graft for 1 to 2 weeks. This method has been described in small series and isolated case reports in combination with graft excision to lower the risk of aortic stump blowout and as a conservative method for treating localized groin infections.<sup>18,19</sup> Morris et al suggested treating graft infection with prolonged, high-dose, local antibiotic irrigation therapy, systemic antibiotic treatment, surgical debridement, and graft conservation.<sup>20</sup> Simple replacement of the prosthesis followed by high-dose systemic antibiotics has not been successful because of the failure of the antibiotics to achieve a minimum inhibitory concentration in the inflamed tissues around the graft. Therefore, these approaches have a limited success, but may be appropriate in the treatment of the occasional high-risk individual.<sup>7,21-23</sup>

The radical treatment consists of TGE, oversewing of the aortic stump, debridement of surrounding tissues, and extra-anatomic bypass grafting.<sup>13,24,25</sup> However, this management is technically complex and is associated with mortality rates of 24% to 70%.<sup>26-34</sup> Other problems with this approach include reduced long-term patency and high amputation rates.<sup>12,13,33,35</sup> In addition, axillofemoral reconstruction may also be associated with the complications of gluteal ischemia, renal failure caused by aortic stump thrombosis, reinfection of the femoral end of the graft, and aortic stump blowout, which is usually fatal. In addition to the high rate of thrombosis, recurrence of infection in the graft occurs in approximately 20% of cases.<sup>33</sup> In view of all these problems, alternative strategies of revascularization have been investigated.



The use of antibiotic-bonded grafts is an attractive surgical adjunct for the treatment of infected aortic prostheses when in situ replacement is deemed feasible. A number of different conduits have been used, including autologous vein,<sup>36-38</sup> cryopreserved arterial allografts,<sup>39</sup> polytetrafluoroethylene,<sup>40,41</sup> and antibiotic-bonded Dacron.<sup>1-4</sup> Initial attempts at in situ replacement with graft and antibiotic combinations were unsuccessful because of the rapid attenuation of drug concentrations in and around the replacement graft site.<sup>42</sup> Coating the prosthesis with a material (collagen or gelatin) to provide a bond between the graft and the antibiotic has enabled such grafts to retain antimicrobial activity for prolonged periods. Rifampicin is a particularly useful antibiotic in this situation, because it has a broad spectrum of activity against gram-negative and gram-positive organisms, especially *S aureus*.<sup>43</sup> It is relatively hydrophobic and therefore does not dissolve into the circulation rapidly. It is also used relatively infrequently in vascular surgery and is less likely to lead to bacterial resistance. Rifampicin-bonded grafts have been shown to be resistant to in vitro infection with *S aureus* for as long as 3 weeks.<sup>44</sup> These factors make TGE and in situ replacement with a rifampicin-bonded prosthesis a feasible option in treating major graft infection. We previously described our initial results with this technique.<sup>3</sup> It has also been used in other centers with good early results.<sup>2,4</sup>

Since publishing our initial results in 5 cases, we have treated six more patients by means of this approach, and we now have a longer follow-up period. Seven patients originally underwent elective repair, and four patients underwent emergency repair. The early (within 30 days) and late mortality rates were 18% and 36%, respectively. Both of the early deaths and one late death occurred in patients who had originally undergone emergency repair of a ruptured abdominal aortic aneurysm (AAA). These figures are comparable with those of a number of other series, which used either extra-anatomic bypass grafting procedures or in situ replacement.<sup>35,45-47</sup> Our results suggest a poorer long-term outcome (75% mortality rate) in the group of patients who had originally undergone emergency procedures. The postoperative mortality rate was also significantly higher in those cases that involved aortoenteric fistulae (3 of 5 presentations), as opposed to one of the remaining 11 presenting symptoms. The long-term mortality rate from graft-enteric fistula has been reported as 48% to 83%.<sup>46-48</sup> This may be because of the acute presentation of these cases and the challenging nature of the subsequent surgery.

However, with regard to other complications, the in situ repairs may fare better. In one recent study, the limb-loss rate was 10% for in situ replacement versus 24% for extra-anatomic bypass grafting procedures.<sup>48</sup> None of the patients in our series sustained limb loss. The limb-loss rate appears to be similarly low with other types of in situ procedure: 6% to 10% for reconstruction with autologous vein<sup>36,50</sup>; 5% for aortic allograft<sup>51</sup>; and 0% for polytetrafluoroethylene replacement.<sup>41</sup> The rate of secondary intervention to salvage limbs was also low in all these groups (0% to 12%). However, the outcome for limb loss or graft revision is less favorable with extra-anatomic bypass grafting procedures, which have amputation rates of 19% to 27%.<sup>13,33,45,52</sup> Extra-anatomic bypass grafting procedures have a risk of 9% to 30% of aortic stump blowout when used in this scenario.<sup>46,49</sup> To date, anastomotic blowout has not been a problem with in situ replacement with a rifampicin-bonded graft, although one patient in our series died as a direct result of aortic candidiasis, which caused aortic rupture above an intact anastomosis.

Another factor that is likely to affect the management of vascular graft infection greatly in the future is MRSA. The proportion of *S aureus* causing hospital-acquired infection that is methicillin resistant has risen from a range of 3% to 5% in the early 1980s to a range of 28% to 54% a decade later.<sup>53-55</sup> Despite the widespread implementation of screening and isolation programs, these multidrug-resistant organisms are becoming increasingly common in surgical and intensive care units. A number of factors have been associated with a predisposition to infection with MRSA, including long-term central venous access, prolonged urinary catheterization, broad spectrum antibiotic use (especially third generation cephalosporins), blood transfusion, and length of preinfection hospital stay.<sup>53-56</sup> All these factors are prevalent in patients undergoing elective and ruptured AAA surgery and increase such patients' risk of acquiring MRSA infection.

The prevalence of *S aureus* infection was relatively low (18%) in our series, whereas others have encountered it in 50% to 86% of cases.<sup>57,58</sup> The two patients with *S aureus* infection in our series had required prolonged intensive care treatment after repair of a ruptured AAA. MRSA was isolated in both of these cases after TGE and in situ replacement. In view of this, we were not able to institute the appropriate high-dose systemic antibiotic regimen from the time of removal and replacement of the prosthesis. The sensitivity of MRSA to rifampicin

is not known, and this may have allowed recolonization of the grafts. Torsello recently reported a death after in situ replacement with a rifampicin-bonded Dacron graft, in which the organism was a multidrug-resistant (including rifampicin) *S aureus*.<sup>2</sup> The dangers of infection by MRSA are highlighted by the eventual death of both of our infected patients; the first died of candidal aortitis and subsequent rupture and the second died of probable MRSA pneumonia after a prolonged period of illness. In our opinion, this poor outcome in patients with MRSA justifies the need for a more aggressive antibiotic regimen (vancomycin, teicoplanin, or both) in cases in which MRSA is likely. However, we are worried about reports emerging on vancomycin- and teicoplanin-resistant strains of MRSA.<sup>59</sup>

Alternative approaches to the treatment of MAGI with MRSA have been reported. Attempts at in situ revascularization with autogenous material,<sup>50</sup> such as lower-extremity veins, have been unsuccessful in the presence of this difficult organism.<sup>60</sup> Accordingly, now when a patient has a suspected MAGI within 3 months of the original procedure (ie, this is probably a virulent organism) or when preoperative cultures are positive for MRSA, our policy is to perform a TGE and extra-anatomic bypass grafting procedure. Until more is known about the effectiveness of the rifampicin-bonded graft in resisting MRSA infection, extra-anatomic bypass grafting is perhaps a safer option, despite its own potential deficiencies.

In four of our early cases, a Foley catheter was placed in the retroperitoneum to allow postoperative irrigation with a solution containing appropriate antibiotics. This technique was abandoned after two of the patients developed severe retroperitoneal candidiasis. This may be related to fungal overgrowth after eradication of the original infecting organism and the prolonged presence of a foreign body. Although we have not found a role for the routine use of retroperitoneal irrigation, we accept that other centers have found it to be beneficial.<sup>6</sup>

In conclusion, our initial optimism about the use of TGE plus in situ replacement with rifampicin-bonded Dacron grafts in the management of major aortic graft infection has been tempered by additional experience. The limitations of the graft in protecting against the growing problem of MRSA infection may limit its usefulness if MRSA becomes even more prevalent and unpredictable in the future.

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